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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.		
10/765,048	01/28/2004	Nobuhiko Nomura	04853.0111	9606		
22852	7590	03/17/2008	EXAMINER			
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP 901 NEW YORK AVENUE, NW WASHINGTON, DC 20001-4413				FETTEROLF, BRANDON J		
ART UNIT		PAPER NUMBER				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,048	NOMURA ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 17 December 2007.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) 1-3 and 6-11 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 4-5 and 12 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) Notice of Informal Patent Application

6) Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 12/17/2007 in response to the previous Non-Final Office Action (9/17/2007) is acknowledged and has been entered.

Claims 1-12 are pending.

Claims 1-3 and 6-11 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 4-5 and 12 are currently under consideration.

Rejections Withdrawn:

The rejection of Claim 4 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements has been withdrawn in view of Applicants amendments.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 4-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pearson et al. (US 5,591,872, 1997, IDS) in view of Smith et al. (J. Immunol. 2001; 167; 366-374, IDS), Koo et al. (US 2002/0054869, 2002, of record) and Rajan et al. (Am. J. Respir. Cell Mol. Biol. 2000; 23: 304-312, of record).

Pearson et al. teach a method of selecting inhibitors of the autoinducer molecule, N-(3-oxododecanoyl) homoserine lactone, comprising contacting the autoinducer molecule with a suspected inhibitor, measuring the ability of the treated autoinducer molecule to stimulate the

activity of a selected gene then determining whether the inhibitor represses or enhances the activity of the autoinducer molecule (column 5, lines 46-55). The patent further teaches a method of inhibiting the infectivity of *P. aeruginosa* and methods of treating an immuno-compromised host infected by *P. aeruginosa*, e.g., a person afflicted with cystic fibrosis (column 6, lines 22-26).

Pearson et al. do not explicitly teach that the method comprising culturing animal cells with the test agent and acylated homoserine lactone and detecting the inhibition of Akt by detecting apoptosis.

Smith et al. teach a method of determining the affects of 3-O-C12- HSL (N-3-oxododecanoyl homoserine lactone) on MAP kinases, comprising contacting 16HBE cells with a test substance such as an inhibitor of the MAP kinase signaling pathway in the presence of 3-O-C12-HSL and determining the activation of ERK (page 371, 1st column, 1st full paragraph to 2nd column). In particular, the reference teaches that 3-O-C12-HSL activates the MAP kinase signaling pathway which is important in IL-8 production (page 371, 1st column, 1st full paragraph). Moreover, the reference teaches that 3-O-C12-HSL also induces NF- κ B and AP-2 which subsequently upregulates IL-8 which leads to neutrophil infiltration and inflammation found in *P. aeruginosa* infection (page 373, 2nd column, last paragraph). Lastly, Smith et al. teach that if structural analogs can be found that antagonize the ability of 3-O-C12-HSL to induce IL-8, they may prove useful therapeutically in cases where exuberant neutrophil responses lead to tissue injury.

Koo et al. teach that inhibition of the MAP kinase signaling pathway specifically triggers an apoptotic response in human cells (paragraph 0010). Koo et al. further teach that inhibitors of the MAP kinase signaling pathway such as PD9805 are useful for inhibiting the growth of a tumor in a mammal, wherein the inhibitor induces a cytotoxic response leading to apoptosis of cells in said mammal (Claims 16-20 of US 2002/0054769).

Rajan et al. teach the induction of apoptosis by *Pseudomonas aeruginosa* in respiratory epithelial cells. In particular, the reference teaches that the resistance of airway epithelial cells to apoptosis is due to the stimulation of NF- κ B by adherent *P. aeruginosa*, wherein NF- κ B appears to have an antiapoptotic effect in respiratory cells.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to culture a test substance in the presence of N-3-oxodocecanoyl homoserine

lactone as taught by Pearson et al. in an animal cell such as a neutrophil and to identify an inhibitor of N-3-oxodocecanoyl homoserine lactone by detecting apoptosis in view of the teachings of Smith et al., Koo et al. and Rajan et al.. One would have been motivated to do so because Smith et al. teaches that 3-O-C12-HSL induces MAP kinases, as well as NF- κ B, each of which are known in the art to be involved in apoptosis in view of the teachings of Koo et al. and Rajan et al.. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by culturing a test substance in the presence of N-3-oxodocecanoyl homoserine lactone as taught by Pearson et al. in an animal cell such as a neutrophil and to identify an inhibitor of N-3-oxodocecanoyl homoserine lactone by detecting apoptosis in view of the teachings of Smith et al., Koo et al. and Rajan et al., one would achieve an effective method of identifying a suitable inhibitor for the treatment of an immunocompromised host infected by *P. aeruginosa*, e.g., a person afflicted with cystic fibrosis.

In response to this rejection, Applicants assert that the claimed invention as a whole is not obvious for at least the reason that the references, whether taken alone or in combination, fail to teach or suggest every element recited in the claims. For example, Applicants assert that Smith does not show anything regarding the Akt signaling pathway and the Examiner has failed to provide any rationale for connecting inhibition of the Raf-MEK-ERK MAP kinase signaling pathway with signaling pathway with "[a] method of screening for a substance the inhibits acylated homoserine lactone, comprising..., detecting one or more of (a) phosphorylated-Akt, wherein increased phosphorylation reflects inhibition of acylated homoserine lactone, (b) apoptosis, or (c) caspase activity, wherein the apoptosis or caspase activity is modulated by Akt and wherein decreased apoptosis or decreased caspase activity reflects inhibition of acylated homoserine lactone" as claimed. Similarly, Applicants assert that Koo fails to mention the Akt pathway or acylated homoserine lactone and the Examiner has again failed to provide any rationale for connecting inhibition of the Raf-MEK-ERK MAP kinase signaling pathway with the claimed method. Thus, Applicants assert that Pearson, Smith, Koo and Rajan, alone or in combination, do not render the instant claims obvious because they do not teach or suggest "detecting one or more of (a) phosphorylated-Akt, wherein increased phosphorylation reflects inhibition of acylated homoserine lactone, (b) apoptosis, or (c) caspase activity, wherein the apoptosis or caspase activity is modulated by Akt and wherein decreased apoptosis or decreased caspase activity reflects inhibition of acylated homoserine lactone", an express step that is recited in the claims. If anything, Applicants assert

that they would suggest to one of skill in the art that inhibitors of acylated homoserine lactone should be screened by assessing the Raf-MEK-ERK MAP kinase signaling pathway, not the Akt signaling pathway.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner acknowledges and does not dispute Applicants assertions that the cited combination is silent on the Akt pathway. However, the Examiner recognizes that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). In the instant case, the Examiner recognizes that Pearson et al. teach a method of selecting inhibitors of the autoinducer molecule, N-(3-oxododecanoyl) homoserine lactone, comprising contacting the autoinducer molecule with a suspected inhibitor, measuring the ability of the treated autoinducer molecule to stimulate the activity of a selected gene then determining whether the inhibitor represses or enhances the activity of the autoinducer molecule, but does not teach that the method occurs in an animal cell or what the gene is or the activity of said gene which is stimulated by an autoinducer molecule and assessed for stimulation or repression by the inhibitor. However, Smith et al. teaches MAP kinase are stimulated by the auto-inducer 3-O-C12-HSL, wherein MAP kinases are known in the art to be involved in apoptosis in view of the teachings of Koo et al. and Rajan et al. Thus, one of ordinary skill in the art would have reasonable expectation of success that by using MAP kinase as the gene stimulated by 3-O-C12-HSL and determining apoptosis in the method taught by Pearson et al. in view of the teachings of Koo et al. and Rajan et al, one would achieve an inhibitor of 3-O-C12-HSL. Thus, the combination of the prior art references appear to teach the same active steps recited in the instant claims, e.g., contacting cells with a test substance in the presence of acylated homoserine lactone and detecting (b) apoptosis. Moreover, the Examiner recognizes that Applicants have put a lot of emphasis on the cited combination being silent on the Akt pathway and conclude that the cited combination would suggest to one of skill in the art that inhibitors of acylated homoserine lactone should be screened by assessing the Raf-MEK-ERK MAP kinase signaling pathway, not the Akt signaling pathway. However, the Examiner recognizes that with the exception of limitation of determining phosphorylated Akt, the claims do not appear to require, *per se*, apoptosis and the Akt

signaling pathway. In other words, Applicants have not provided a patentable difference between determining apoptosis as a result on the Raf-MEK-ERK MAP signaling pathway and determining apoptosis as a result of the Akt pathway, since all the claims require is determining apoptosis.

Claims 4-5 and 12 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pearson et al. (US 5,591,872, 1997, IDS) in view of Telford et al. (Infection and Immunity, 1998; 36-42, of record) and Maianski et al. (Blood, 2002; 101: 1987-1995, prepublished online as Blood First Edition Paper, October 10, 2002, of record).

Pearson et al. teach a method of selecting inhibitors of the autoinducer molecule, N-(3-oxododecanoyl)homoserine lactone, comprising contacting the autoinducer molecule with a suspected inhibitor, measuring the ability of the treated autoinducer molecule to stimulate the activity of a selected gene then determining whether the inhibitor represses or enhances the activity of the autoinducer molecule (column 5, lines 46-55). The patent further teaches a method of inhibiting the infectivity of *P. aeruginosa* and methods of treating an immuno-compromised host infected by *P. aeruginosa*, e.g., a person afflicted with cystic fibrosis (column 6, lines 22-26).

Pearson et al. do not explicitly teach that the method comprising culturing animal cells with the test agent and acylated homoserine lactone and detecting the inhibition of Akt by detecting apoptosis or caspase activity.

Telford et al. teach that the *Pseudomonas aeruginosa* Quorum-Sensing Signal Molecule N-(3-Oxodocecanoyl)-L-homoserine Lactone has immunomodulatory activity and inhibits the production of tumor necrosis factor alpha by lipopolysaccharide-stimulated macrophages (abstract).

Maianski et al. teach that the mechanism of apoptosis induction by TNF- $\square\blacksquare$ is closely related to the cascade of apoptotic cysteine proteases known as caspases which represent a group of enzymes responsible for initiation and execution of apoptosis, wherein TNF- $\square\blacksquare$ induces apoptosis through the activation of caspases (page 1987, 1st column, 2nd full paragraph and page 1993, 2nd column, 2nd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to culture a test substance in the presence of N-3-oxodocecanoyl homoserine lactone as taught by Pearson et al. in an animal cell such as a neutrophil and to identify an inhibitor

of N-3-oxodocecanoyl homoserine lactone by detecting apoptosis or caspases activity in view of the teachings of Telford et al. and Maianski et al.. One would have been motivated to do so because Telford et al. teaches that 3-O-C12-HSL inhibits TNF- α production which is well known in the art to be involved in apoptosis via the activation of caspases as taught by Maianski et al. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by culturing a test substance in the presence of N-3-oxodocecanoyl homoserine lactone as taught by Pearson et al. in an animal cell such as a neutrophil and to identify an inhibitor of N-3-oxodocecanoyl homoserine lactone by detecting apoptosis or caspase activity in view of the teachings of Telford et al. and Maianski et al., one would achieve an effective method of identifying a suitable inhibitor for the treatment of an immuno-compromised host infected by *P. aeruginosa*, e.g., a person afflicted with cystic fibrosis.

In response to this rejection, Applicants reiterate the arguments set forth above that the prior art, whether taken alone or in combination, fail to teach or suggest every element recited in the claims.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above and incorporated herein.

Therefore, NO claim is allowed

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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